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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,782	07/09/2001	Susan Hardin	0007/01 UTL	9388

7590 09/10/2003

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EXAMINER

SMITH, CAROLYN L

ART UNIT	PAPER NUMBER
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1631

21

DATE MAILED: 09/10/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/901,782

Applicant(s)

HARDIN ET AL.

Examiner

Carolyn L Smith

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 April 2003 and 20 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34 is/are pending in the application.
- 4a) Of the above claim(s) 25-34 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-34 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 17. 6) ☐ Other:

DETAILED ACTION

Applicants' amendments and remarks in Paper No. 16 and 20, filed 4/3/03 and 6/20/03, are acknowledged. Amended claims 1, 7, 10, 16, and 20 are acknowledged. The species election requirement is hereby withdrawn as generic claim 10 appears to be free of the prior art.

Applicants' arguments, filed 4/3/03, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821 (a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR § 1.821 through 1.825, because many, if not all, of the newly added SEQ ID NOs (to the specification) do not correspond to the sequences in the Sequence Listing, particularly SEQ ID NO: 11. Applicant(s) are required to submit a new computer readable form sequence listing, a paper copy, or CD-ROM for the specification, statements under 37 CFR § 1.821 (f) and (g), if there is a need to list additional sequences in the sequence listing. Applicant(s) are given the same response time regarding this failure to comply as that set forth to respond to this office action. Failure to respond to this requirement may result in abandonment of the instant application or a notice of a failure to fully respond to this Office Action.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The present title is directed to real-

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time sequence determination a method-type invention whereas in contrast the elected claims include a composition of the polymerizing agent type.

Claims 1-24 are herein under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an interaction of tags relating to acceptor and donor interactions, does not reasonably provide enablement for other types of interactions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to make and use the invention commensurate in scope with these claims. The specification provides enablement for detecting extension products containing a fluorescent tag (p. 3, line 9), using dye-terminator chemistry with donor and acceptor dyes (p. 3, lines 21-32), including a donor-acceptor pairs (p. 20, lines 20-23). The breadth of the claims encompasses a broader set of interactions which is not sufficiently enabled in the specification.

Claims Rejected Under 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 6, 16, 18, 19, and 24 is maintained under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claims 6 (line 3), 19 (line 3), and 24 (line 3) recite the phrase “mixtures or combinations thereof of the *Taq* polymerase” which is vague and indefinite. It is unclear what else may be included in these multiple entities besides *Taq* DNA polymerase I. Clarification of the metes and bounds of these claims via clearer claim wording is required.

Claim 10 is rejected due to the lack of clear antecedent basis for “the polymerase” and the polymerizing agent, on line 5. The claim begins by stating “a polymerizing agent” to include both “the polymerase” and a monomer. The last mention of “polymerizing agent” is separate from the monomer. Clarification of these discrepancies via clearer claim wording is required. Claims 11-19 are also rejected due to their direct or indirect dependency from claim 10.

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Claim 16 is vague and indefinite due to the unclarity of citing an abbreviation, such as dNTP on line 1. Correction is suggested by amending in of the full name in parentheses. Claim 18 is also rejected due to its dependency from claim 16.

Claim 16, line 2, recites the term "group" which is vague and indefinite. It is unclear which entity the "group" is a part of, the polymerase, the monomer, or the dNTP. Clarification of the location of the "group" is required. Claim 18 is also rejected due to its dependency from claim 16.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent,
- (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States,
- (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 7-9, and 20-23 are rejected under 35 U.S.C. 102(a) and (b) as being anticipated by Williams (WO 00/36151 under 102(a)) and Brandis (Nucleic Acids Research, 1999, Vol. 27, No. 8 under 102(b)).

Applicants state the critical difference between their invention and the prior art is that the tags in their invention remain associated with the polymerizing agent. This is found unpersuasive as the claims, as written, state a polymerizing agent and a tag without mention of

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whether this tag is transient or permanent. Applicants state the Williams/Brandis prior art references do not disclose a tagged polymerizing agent. This is found unpersuasive as bonding inherently occurs between the polymerase and the tagged entity, as will be further described, *infra*. Even though this bonding may occur transiently, it does occur which is encompassed in the broad reasonable interpretation of the tagged polymerase agent.

Williams discloses a *Taq* DNA polymerase (p. 8, lines 23-28) in which a fluorescently labeled dNTP (tag) is associated with the polymerase during monomer incorporation (p. 8, lines 1-9). Williams discloses a fluorophore and quencher pair being incorporated into oligo probes (p. 2, lines 16-18). The dNTP tag consists of a labeled nucleotide triphosphate (NTP) having a γ -phosphate with a fluorophore moiety attached and a quencher moiety that sufficiently prevents fluorescence until incorporation of the NTP at which time the γ -phosphate with the fluorophore moiety is released and detected (p. 8, lines 10-20). As Webster's II New Riverside Dictionary defines a tag as a piece of something that identifies, classifies or labels; one reasonable interpretation of the quencher is a tag whose close presence to the fluorophore tag results in fluorescent signal disappearance (p. 2, lines 16-25). Williams discloses the fluorescence is detected when labeled dNTPs are incorporated into the strand and fluorescence is induced (p. 9, lines 28-29). Williams discloses that upon incorporation, the fluorescent dye molecule is released with pyrophosphate from the polymerase and then swept away from the parent DNA molecule by the flow (p. 10, lines 13-17), suggesting the polymerase's detectable property reverts back to its initial state. Williams discloses that as the polymerase moves along the DNA, the nucleotide sequence is read from the order of released dyes (p. 14, lines 30-31). Williams

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discloses the possible presence of other polymerases, such as HIV reverse transcriptase, as stated in claims 5, 9, and 23.

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to show that a characteristic not disclosed in the reference is inherent (see MPEP 2131.01 (c)). Brandis discloses a *Taq* DNA polymerase I including an inherent characteristic that polymerases go through conformational changes (abstract). Brandis also discloses that a change occurs in a fluorescent label during the change in conformational states of the polymerase when nucleotide binding occurs as the polymerase is active (abstract). Voet et al. disclose a transition state theory allowing the understanding of how enzymes catalyze reactions (p. 332, col. 2, first paragraph). Voet et al. disclose a high-energy (unstable) complex existing with covalent bonds during a bimolecular reaction (p. 332, col. 2, second paragraph).

Thus, Williams and Brandis anticipate claims 1-5, 7-9, and 20-23 of the instant invention.

Claims 1, 3, and 4 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Patel et al. (P/N 6,329,178).

Applicants state Patel et al. do not disclose tagged polymerases that undergo a change during monomer incorporation. This is found unpersuasive as claims 1, 3, and 4 are directed to a composition of a polymerizing agent including a tag which has detectable properties that can undergo a change. Covalent bonding is an inherent characteristic that occurs during monomer incorporation (as further described, *infra*). During this bonding process, the polymerases are attached to the tags, albeit transiently. Applicants cite other instances, such as certain regions of the polymerase and using cysteine as the mutant amino acid, as major differences between the

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Patel et al. reference and the instant invention. This is found unpersuasive as these limitations are not addressed in the instantly rejected claims 1, 3, and 4.

Patel et al. disclose the *Taq* DNA polymerase I (col. 13, lines 5-8) active site is highly mutable and can accommodate many amino acid substitutions without significantly affecting activity (col. 2, lines 63-66). Patel et al. disclose that mutant DNA polymerases can incorporate unconventional nucleotides (col. 3, lines 44-48), such as bases labeled with a reporter molecule and fluorescently labeled bases (col. 6, lines 14-19) which suggests types of tags. Patel et al. disclose the fluorescently labeled tags exhibiting different emissions when a DNA fragment is extended by DNA polymerase (col. 10, lines 38-67). Patel et al. disclose a polymerase having enzymatic properties featuring catalytic activities (col. 5, lines 1-20).

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to show that the characteristic not disclosed in the reference is inherent (see MPEP 2131.01(c)). Voet et al. disclose a transition state theory allowing the understanding of how enzymes catalyze reactions (p. 332, col. 2, first paragraph). Voet et al. disclose a high-energy (unstable) complex existing with covalent bonds during a bimolecular reaction (p. 332, col. 2, second paragraph).

Thus, Patel et al. anticipate claims 1, 3, and 4.

Claims 1, 2, 3, and 7 are rejected under 35 U.S.C. 102(e)(2) as being anticipated by Allen (P/N 6,280,939).

Allen discloses a polymerase that produces motions detectable during monomer incorporation (abstract). These motions are caused while the polymerase incorporates

nucleotides into a chain and the newly formed nucleotide strand translocates through the polymerase's reaction site (abstract). Allen discloses detecting these conformational changes in motion (data collection) after the DNA/polymerase complex has formed and the polymerization temperature is reached (col. 15, lines 26-42). The continuous stream of reaction data as represented in Figures 3 and 5 (note the detection peaks as incorporation occurs in the top 4 rows of Figure 3) [as well as col. 4, lines 28-45], as one nucleotide is incorporated at a time shows that changes from first state and first value to second state and value and back to first state and value before, during, and/or after monomer incorporation as stated 1 and 2. Allen discloses placing an atomic force microscopic probe tip placed at a polynucleotide/polymerase complex to detect the polymerase motion changes (col. 4, lines 3-14). Allen discloses the DNA template rests in the polymerase reaction site in the polynucleotide/polymerase complex (col. 5, lines 49-54). Allen discloses conformational changes of the polymerase structure in the complex that occur during the polymerase reaction (col. 6, lines 45-65) which represent a type of molecular tag indicating change based on motion detection.

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when extra references are cited to show that the characteristic not disclosed in the reference is inherent (see MPEP 2131.01(c)). Voet et al. disclose a transition state theory allowing the understanding of how enzymes catalyze reactions (p. 332, col. 2, first paragraph). Voet et al. disclose a high-energy (unstable) complex existing with covalent bonds during a bimolecular reaction (p. 332, col. 2, second paragraph).

Thus, Allen anticipates the limitations in claims 1, 2, 3, and 7.

Conclusion

No claim is allowed.

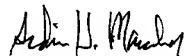
Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (703) 308-6043. The examiner can normally be reached Monday through Friday from 8 A.M. to 4:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

September 4, 2003


ARDIN H. MARSCHEL
PRIMARY EXAMINER